RULE 132 DECLARATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of
Noboru Abe, et al.
Serial No.: 10/584,221 Art Unit 1621
Confirmation No.: 1699 Examiner Valenrod, Yevgeny
Filed: June 20, 2007
For: PROCESS FOR PRODUCING 2-HALOGENOBENZAMIDE COMPOUND

D E C L A R A T I O N

Honorable Commissioner for
Patents and Trademarks
Alexandria, VA 22313-1450

Sir:

I, Hiroki Kodama, a citizen of Japan, residing 685 Tohkikita, Naka-ku, Sakai-shi, Japan, declare:

THAT I graduated from Osaka Prefectural College of Technology in March 1980;

THAT I entered NIHON NOHYAKU CO., LTD. in April 1980, and I have been working in PROCESS RESEARCH UNIT of R & D STRATEGY DEPARTMENT OF RESEARCH & DEVELOPMENT DIVISION of said company;

THAT I am one of the co-inventors of the above-identified application, and familiar with the disclosure and the claims of the said application;

THAT I have read and understood the Offica Action with the mailing date of July 6, 2009;

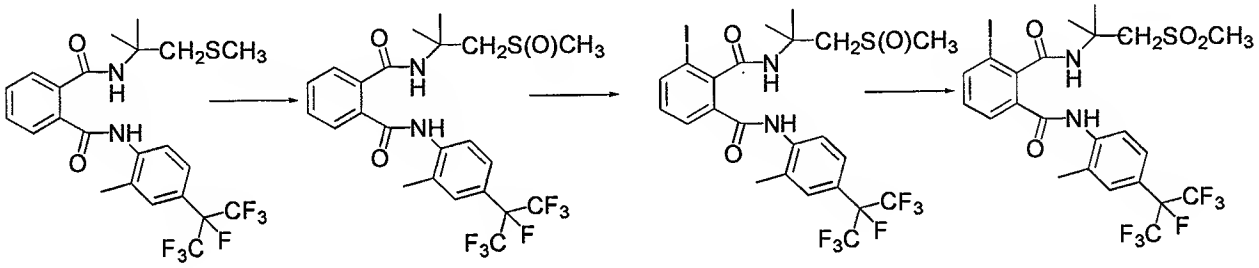
THAT in order to clarify the superiority of the invention of the above-identified application, I conducted the following experiment:

I. Experimental

Yield of a 2-halogenobenzamide compound obtained in the present inventive route was compared with two routes derivable from the prior art employing the identical starting material and reaction conditions

Specific procedure of each route is hereinafter detailed.

1. Sulfide⇒Sulfoxide⇒Halogenated sulfoxide⇒Halogenated sulfone (Present inventive route)



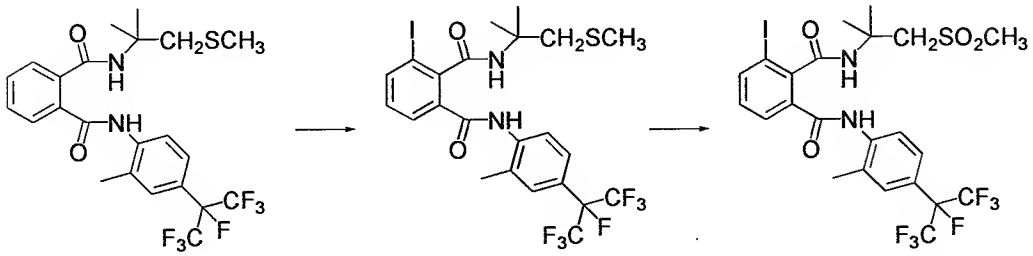
N^2-[1,1-dimethyl-2-(methylthio)ethyl]-N^1-{2-methyl-4-{1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl}phenyl}-1,2-benzenedicarboxamide (52.4 g, 0.10 mol) was dissolved in 1,2-dichloroethane (100ml). 88% Formic acid (0.94 g, 0.023 mol) was added to this solution, followed by adding dropwise thereto 35% hydrogen peroxide (10.7 g, 0.11 mol) at 60°C. After completion of the dropwise addition, the resulting mixture was stirred at 60°C for 1 hour and an aqueous sodium sulfite solution was added dropwise to the thus obtained reaction mixture at the same temperature to decompose the excess oxidizing agent. Then, the resulting mixture was neutralized with an aqueous sodium hydrogencarbonate solution, after which the organic layer was separated. The organic layer obtained was slowly cooled to 20°C. The crystals precipitated were filtered to obtain 50.8 g (94% yield) of N^2-[1,1-dimethyl-2-(methylsulfinyl)ethyl]-N^1-{2-methyl-4-{1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl}phenyl}-1,2- benzenedicarboxamide.

The obtained N^2-[1,1-dimethyl-2-(methylsulfinyl)ethyl]-N^1-{2-methyl-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]phenyl}-1,2-benzenedicarboxamide was dissolved in N,N-dimethylacetamide (200 mL). 1,3-diiodo-5,5-dimethylhydantoin (19.8 g, 0.052 mol) and palladium acetate

(0.045 g, 0.002 mol) was added to this solution, and then stirred with heating at 80°C for 3 hours. The solvent was distilled off under reduced pressure and the resulting concentrate was dissolved in 1,2-dichloroethane (200 mL). The resulting solution was washed with an aqueous sodium thiosulfate solution and water. About 96% (HPLC area percent) of N^2-[1,1-dimethyl-2-(methylsulfinyl)ethyl]-3-iodo-N^1-{2-methyl-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]phenyl}-1,2-benzenedicarboxamide was contained in the obtained organic layer. The solution was used in the next step without further purification.

To this solution were added 88% formic acid (5.25 g,0.1 mol) and concentrated sulfuric acid (3.92 g, 0.04 mol), and to the resulting mixture was added dropwise 35% hydrogen peroxide (11.8 g,0.12 mol) at 60°C. After stirring at the same temperature for 1 hour, an aqueous sodium sulfite solution was added to the reaction mixture to decompose the excess oxidizing agent. The reaction mixture was cooled and then neutralized with an aqueous sodium hydroxide solution, and the crystals precipitated were filtered, washed with water and then dried to obtain 57.3 g (84% yield from starting material) of N^2-[1,1-dimethyl-2-(methylsulfonyl)ethyl]-3-iodo-N^1-{2-methyl-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]phenyl}-1,2-benzenedicarboxamide.

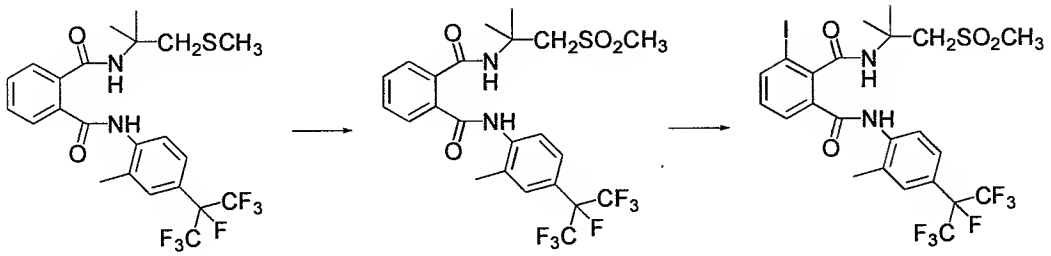
2. Sulfide⇒Halogenated sulfide⇒Halogenated sulfone (Route 2 - 1st derivable route from the prior art)



N^2-[1,1-dimethyl-2-(methylthio)ethyl]-N^1-{2-methyl-4-{1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl}phenyl}-1,2-benzenedicarboxamide (52.4 g, 0.10 mol) was dissolved in N,N-dimethylacetamide (200 mL). 1,3-diiodo-5,5-dimethylhydantoin (19.8 g, 0.052 mol) and palladium acetate (0.045 g, 0.002 mol) was added to this solution, and then stirred with heating at 80°C for 3 hours. The solvent was distilled off under reduced pressure and the resulting concentrate was dissolved in 1,2-dichloroethane (200 mL). The resulting solution was washed with an aqueous sodium thiosulfate solution and water. About 30% (HPLC area percent) of N^2-[1,1-dimethyl-2-(methylthio)ethyl]-3-iodo-N^1-{2-methyl-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]phenyl}-1,2-benzenedicarboxamide was contained in the obtained organic layer. The organic layer was concentrated in vacuo and purified by silica gel column chromatography to obtain 17.6 g (27% yield) of N^2-[1,1-dimethyl-2-(methylthio)ethyl]-3-iodo- N^1-{2-methyl-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]phenyl}-1,2-benzenedicarboxamide.

N^2-[1,1-dimethyl-2-(methylthio)ethyl]-3-iodo- N^1-{2-methyl-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]phenyl}-1,2-benzenedicarboxamide obtained above was dissolved in 1,2-dichloroethane (60ml). To this solution were added 88% formic acid (3.16 g,0.06 mol) and concentrated sulfuric acid (2.36 g, 0.024 mol), and to the resulting mixture was added dropwise 35% hydrogen peroxide (7.08 g,0.072 mol) at 60°C. After stirring at the same temperature for 1 hour, an aqueous sodium sulfite solution was added to the reaction mixture to decompose the excess oxidizing agent. The reaction mixture was cooled and then neutralized with an aqueous sodium hydroxide solution, and the crystals precipitated were filtered, washed with water and then dried to obtain 17.1 g (25% yield from starting material) of N^2-[1,1-dimethyl-2-(methylsulfonyl)ethyl]-3-iodo- N^1-{2-methyl-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]phenyl}-1,2-benzenedicarboxamide.

3. Sulfide⇒Sulfone⇒Halogenated sulfone (Route 3 - 2nd derivable route from the prior art)



N^2-[1,1-dimethyl-2-(methylthio)ethyl]-N^1-{2-methyl-4-{1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl}phenyl}-1,2-benzenedicarboxamide (52.4 g, 0.10 mol) was dissolved in 1,2-dichloroethane (100ml). To this solution were added 88% formic acid (5.25 g, 0.1 mol) and concentrated sulfuric acid (3.92 g, 0.04 mol), and to the resulting mixture was added dropwise 35% hydrogen peroxide (23.6 g, 0.24 mol) at 60°C. After completion of the dropwise addition, the resulting mixture was stirred at 60°C for 1 hour and an aqueous sodium sulfite solution was added dropwise to the thus obtained reaction mixture at the same temperature to decompose the excess oxidizing agent. Then, the resulting mixture was neutralized with an aqueous sodium hydrogencarbonate solution, after which the organic layer was separated. The organic layer obtained was slowly cooled to 20°C. The crystals precipitated were filtered to obtain 53.4 g (yield 96%) of N^2-[1,1-dimethyl-2-(methylsulfonyl)ethyl]-N^1-{2-methyl-4-{1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl}phenyl}-1,2- benzenedicarboxamide.

The obtained N^2-[1,1-dimethyl-2-(methylsulfonyl)ethyl]-N^1-{2-methyl-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]phenyl}-1,2-benzenedicarboxamide was dissolved in N,N-dimethylacetamide (200 mL). 1,3-diiodo-5,5-dimethylhydantoin (19.8 g, 0.052 mol) and palladium acetate (0.045 g, 0.002 mol) was added to this solution, and then stirred with heating at 80°C for 3 hours. The solvent was distilled off under reduced pressure and the resulting concentrate was dissolved in 1,2-dichloroethane (200 mL). The resulting solution was washed with an aqueous sodium thiosulfate solution and water. N^2-[1,1-dimethyl-2-(methylsulfonyl)ethyl]-3-iodo-N^1-{2-methyl-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]phenyl}-1,2-benzenedicarboxamide was not contained in the obtained organic layer.

II. Results and discussion

The results are as shown I the below table.

Route*	Yield of target compound
1 (Present)	84%
2 (Prior art)	25%
3 (Prior art)	0%

*Route 1: Present inventive route
(Sulfide⇒Sulfoxide⇒Halogenated sulfoxide⇒Halogenated sulfone)
Route 2: 1st derivable route from the prior art
(Sulfide⇒Halogenated sulfide⇒Halogenated sulfone)
Route 3: 2nd derivable route from the prior art
(Sulfide⇒Sulfone⇒Halogenated sulfone)

As is understood from the above table, the yield of the present invention as indicated by Route 1, achieved far higher yield of the target compound compared with the other routes conceivable from the prior art documents.

The present invention therefore can exert remarkably superior effect to the prior art.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 5th day of November 2009

Hiroki Kodama

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